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Modulation of 11 β -Hydroxysteroid Dehydrogenase as a Strategy to Reduce Vascular Inflammation

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Abstract Atherosclerosis is a chronic inflammatory disease in which initial vascular damage leads to extensive macrophage and lymphocyte infiltration. Although acutely glucocorticoids suppress inflammation, chronic glucocorticoid excess worsens atherosclerosis, possibly by exacerbating systemic cardiovascular risk factors. However, glucocorticoid action within the lesion may reduce neointimal proliferation and inflammation. Glucocorticoid levels within cells do not necessarily reflect circulating levels due to pre-receptor metabolism by 11 β -hydroxysteroid dehydrogenases (11 β -HSDs). 11 β -HSD2 converts active glucocorticoids into inert 11-keto forms. 11 β -HSD1 catalyses the reverse reaction, regenerating active glucocorticoids. 11 β -HSD2-deficiency/ inhibition causes hypertension, whereas deficiency/ inhibition of 11 β -HSD1 generates a cardioprotective lipid profile and improves glycemic control. Importantly, 11 β -HSD1-deficiency/ inhibition is atheroprotective, whereas 11 β -HSD2-deficiency accelerates atherosclerosis. These effects are largely independent of systemic risk factors, reflecting modulation of glucocorticoid action and inflammation within the vasculature. Here, we consider whether evidence linking the 11 β -HSDs to vascular inflammation suggests these isozymes are potential therapeutic targets in vascular injury and atherosclerosis.

Keywords Atherosclerosis · Neointima · Inflammation · Glucocorticoid · 11 β -Hydroxysteroid dehydrogenase

Abbreviations

| | |
|-----------------|--|
| 11 β -HSD | 11 β -Hydroxysteroid dehydrogenase |
| GR | glucocorticoid receptor |
| MR | mineralocorticoid receptor |

Introduction

Atherosclerosis is widely acknowledged to be an inflammatory disease, with lesions resulting from an unchecked wound healing response to chronic arterial injury. Extensive inflammatory cell (macrophage and lymphocyte) invasion of the sub-endothelial space is key to lesion development [1–5]. Consequently, glucocorticoids, which are potent anti-inflammatory agents, might be expected to inhibit atherogenesis. In fact, glucocorticoid excess, whether endogenous (Cushing's disease) or through pharmacotherapy, is associated with increased atherosclerosis and cardiovascular events [6–9], probably due, at least in part, to glucocorticoid-mediated exacerbation of systemic cardiovascular risk factors (including insulin resistance/type 2 diabetes, hypertension and dyslipidaemia). However, most atherosclerosis occurs independently of exogenous glucocorticoid administration, and plasma levels of glucocorticoids are not normally elevated in atherosclerosis. Nevertheless, recent evidence implicates cell-specific modulation of glucocorticoid action *within* the vasculature in this condition.

Glucocorticoid delivery and action within tissues can be modulated at a number of levels beyond the hypothalamic-pituitary-adrenal axis. Normally, the majority of plasma glucocorticoid (cortisol or corticosterone) is bound to the high affinity, but finite capacity, corticosterone binding globulin (CBG), leaving ~5 % being "free" and accessible to tissues. The mineralocorticoid aldosterone, and the

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intrinsically inactive 11-keto glucocorticoids cortisone and 11-dehydrocorticosterone, bind poorly to CBG, so that free concentrations are similar to free cortisol/corticosterone levels. However, CBG may not simply be an inert carrier; it can be cleaved by neutrophil elastase, releasing cortisol/corticosterone at sites of inflammation, thus potentially acting as a targeted glucocorticoid delivery mechanism [10]. Once inside cells, glucocorticoids can be actively removed by membrane pumps such as MDR1 [11], metabolised by 11 β -hydroxysteroid dehydrogenase (11 β -HSD; see below), or can bind to and activate cognate receptors, glucocorticoid receptor (GR) and, in cells which lack 11 β -HSD2 (see below), the higher affinity mineralocorticoid receptor (MR). Activated receptors translocate to the nucleus to transcriptionally regulate specific gene networks.

Although all these mechanisms represent potential druggable targets in atherosclerosis, recent evidence points to the type 1 11 β -HSD enzyme, which in vivo predominantly converts intrinsically inert glucocorticoids (cortisone, 11-dehydrocorticosterone) into corresponding active forms (cortisol, corticosterone), as a particularly attractive target [12]. Inhibition of 11 β -HSD1 is atheroprotective, at least in animal models. Conversely, inactivation of renal 11 β -HSD type 2 (11 β -HSD2), which catalyses the opposite reaction, inactivating glucocorticoids in vivo, is well established as a cause of hypertension in humans. Recent data have shown that 11 β -HSD2-deficiency worsens atherosclerosis independently of effects on hypertension [13•]. Here, we assess the potential of 11 β -HSD1 as a therapeutic target in atherosclerosis by reviewing the actions of 11 β -HSDs on vascular inflammation, considering local effects on the vasculature as well as effects on systemic cardiovascular risk factors.

Glucocorticoids and Cardiovascular Risk

To understand the potential benefits of 11 β -HSD modulation in vascular inflammation, it is essential first to consider the actions of glucocorticoids. The complex relationship between glucocorticoids and cardiovascular disease is incompletely understood and may differ between humans and animal models (recently reviewed in [14–16]). Some of this complexity undoubtedly arises from the diverse actions of glucocorticoids: direct effects of glucocorticoids with the heart and vasculature may be largely beneficial, at least within certain cell types, whereas adverse effects may be mediated indirectly by changes in systemic risk factors (such as hypertension, lipids and insulin resistance/ diabetes).

The effect of glucocorticoids on dyslipidaemia and other systemic risk factors has been established for over 60 years [17–19]. Consistent with exacerbation of systemic risk factors, endogenous glucocorticoid excess or glucocorticoid

pharmacotherapy in humans are associated with increased extent and severity of atherosclerosis, and predict cardiovascular morbidity and mortality [5, 20–28]. Discontinuation of glucocorticoid pharmacotherapy reduces cardiovascular risk [6, 29]. Similarly, normalisation of circulating glucocorticoids in Cushing's disease largely reverses pathophysiological changes in vascular function and structure [9]. However, hyperglycaemia and dyslipidaemia are only modestly improved within the same time frame, suggesting distinct beneficial effects of reducing glucocorticoid action separate from effects on the classical systemic risk factors [9].

In contrast, animal studies suggest that glucocorticoids reduce atherosclerosis, despite causing hyperlipidaemia [30–40]. Furthermore, a recent report elegantly demonstrated that 'painting' dexamethasone onto atherosclerotic lesions improved markers of plaque stability (reducing macrophage content and increasing fibrous cap thickness) [41]. This discrepancy between the atherosclerosis-promoting effects of glucocorticoids in humans but not in animals remains unexplained, but may be related to the predominant use of dexamethasone as the glucocorticoid of choice in animals. Whereas endogenous glucocorticoids are agonists at both GR and MR, synthetic glucocorticoids, including dexamethasone, poorly activate MR. Chronically increased mineralocorticoid action, even at relatively modest levels, appears pro-inflammatory within the cardiovascular system, distinct from effects of MR activation upon blood pressure [42].

Glucocorticoids and the Acute Vascular Response to Injury

The introduction of percutaneous angioplasty for treatment of occluded arteries highlighted the fibroproliferative vascular response to acute mechanical injury. Indeed, re-occlusion (restenosis) of atherosclerotic arteries following angioplasty is a clinically significant complication of the technique. Acute arterial injury (eg by insertion of a wire or stent, by ligation, or with a laser) in animals provides a tool to elucidate the mechanisms underlying restenosis in atherosclerosis as well as exploring novel treatments. Mechanical arterial injury provokes an influx of inflammatory cells, recruited by factors such as monocyte-chemoattractant protein (MCP)-1 released from the injured vascular/endothelial cells [43], which stimulates proliferation and migration of vascular smooth muscle cells, forming the neointima [44]. Inhibition of this inflammatory response has been central to the use of glucocorticoids as potential inhibitors of neointimal lesion formation/restenosis [45–50].

Despite the largely positive data obtained in animals, clinical use of glucocorticoids (methylprednisolone, dexamethasone) for prevention of restenosis was initially disappointing [51–55]. However, recent trials are promising

[56–59], reporting beneficial effects of prednisone [59, 60] or dexamethasone [55, 61]. It is not clear whether discrepancies between clinical and pre-clinical studies are due to animal models providing poor representations of human disease or reflect limitations in clinical trials (eg small group sizes, patient selection; route of administration). Alternatively, the discrepancies may result from a different balance in rodents and humans between the adverse effects of glucocorticoids upon systemic risk factors and beneficial effects on vascular inflammation, with the balance more in favour of the former in humans. Moreover, any systemic therapy will depress HPA axis activity, altering the balance of *endogenous* glucocorticoid ligands. Thus, identification of the cellular and molecular (eg MR or GR) targets of glucocorticoid action, including endogenous glucocorticoids, during vascular inflammation is crucial to development of novel, better targeted therapies.

Metabolism by 11 β -HSDs Modulates Glucocorticoid Action

Glucocorticoid action within cells depends upon receptor density and ligand availability. The latter is potentially influenced by the 11 β -HSD isozymes. 11 β -HSD1 is co-localised in the lumen of the endoplasmic reticulum with hexose-6-phosphate dehydrogenase which, by coupling glucose-6-phosphate oxidation to reduction of NADP⁺, generates the high NADPH/NADP⁺ ratio required to drive 11 β -HSD1 reductase activity [62], converting inert cortisone and 11-dehydrocorticosterone into active cortisol and corticosterone, respectively. 11 β -HSD2 is exclusively a dehydrogenase, inactivating glucocorticoids [63]. Some synthetic glucocorticoids, notably prednisolone/prednisone, are also substrates for the 11 β -HSDs and are readily interconverted *in vivo*. Others, including dexamethasone, are poorly metabolised by these enzymes. Both isozymes are inhibited by the liquorice derivative, glycyrrhetic acid or its synthetic analogue, carbenoxolone, which have contributed greatly to our current understanding of the function of 11 β -HSDs, especially in humans. More recently, selective 11 β -HSD1 inhibitors have been developed, allowing much greater discrimination of the roles of these important enzymes [64].

The 11 β -HSDs are Expressed in the Cardiovascular System

11 β -HSD1 is widely expressed, with highest expression in the liver and more modest expression elsewhere, typically in classical glucocorticoid target cells and tissues [63]. During pathogenesis, expression is increased at some sites, notably in adipose tissue in obesity and at sites of inflammation (see below). In contrast, 11 β -HSD2 expression is restricted to mineralocorticoid target cells/tissues, including the distal

nephron, and limited other sites such as the skin, lung and adrenal cortex [65]. Both isozymes are modestly expressed in the vasculature; 11 β -HSD1 is probably restricted to vascular smooth muscle cells, with 11 β -HSD2 expressed in the endothelium (reviewed in [15, 16]). Some studies have reported 11 β -HSD2 expression in the vascular smooth muscle cells [66] and 11 β -HSD1 in the endothelium [67•], though these studies depend on antibody specificity and others have not confirmed these findings [68]. Whilst co-expression cannot be excluded, normally 11 β -HSD isozyme expression is mutually exclusive within individual cells.

The 11 β -HSDs Modulate Cardiovascular Disease Risk Factors

Both 11 β -HSD isozymes modulate systemic cardiovascular risk factors, with a well-established role for 11 β -HSD2 in regulating mineralocorticoid effects, including blood pressure, and with 11 β -HSD1 implicated in the pathogenesis of metabolic syndrome.

By inactivating glucocorticoids, 11 β -HSD2 activity confers mineralocorticoid-specificity upon MR in cells in which they are co-expressed. Deficiency in, or inhibition of, 11 β -HSD2 allows inappropriate activation of MR by glucocorticoids, causing the syndrome of Apparent Mineralocorticoid Excess, characterised by hypertension, hypokalaemia and suppression of the renin-angiotensin-aldosterone system [69].

A physiological role for 11 β -HSD1 has been slower to emerge. However, over the last decade it has become apparent that amplification of intracellular glucocorticoid levels by 11 β -HSD1, especially in adipose tissue and/or brain, contributes to obesity-associated metabolic disease and age-related cognitive decline (reviewed in [70]). 11 β -HSD1 expression in adipose tissue is selectively elevated in obese humans and in rodents with monogenic obesity. Inhibition of 11 β -HSD1 reduces levels of plasma glucose, glycated haemoglobin A1c (HbA1c) and cholesterol in patients with type 2 diabetes [71] and 11 β -HSD1-deficiency or inhibition improves insulin sensitivity in animal models of diabetes and/or obesity [63]. Conversely, in mice, transgenic over-expression of 11 β -HSD1 selectively in adipose tissue produces local, but not systemic, glucocorticoid excess and causes visceral obesity, hypertension, diabetes and dyslipidaemia [72, 73], whereas over-expression in liver causes hypertension and mild insulin resistance [74].

In a similar manner, age-related cognitive decline (itself associated with impaired glycaemic control [75]) is associated with higher 11 β -HSD1 activity in humans [76] and in rodents [77], and 11 β -HSD1-deficient mice are protected from age-related cognitive decline (reviewed in [78]). A causative role is supported by the phenotype of transgenic mice with selective over-expression of 11 β -HSD1 in fore-brain, which develops cognitive deficits at an earlier age

than wild-type controls [77]. In humans, age-related cognitive decline, diabetes and metabolic syndrome, like atherosclerosis, are all associated with increased markers of inflammation, including in macrophages (or microglia in the brain). It is conceivable that altered inflammatory responses underlie at least part of the effects of 11 β -HSD1 manipulation.

11 β -HSDs and Inflammation

11 β -HSD1 and 11 β -HSD2 show opposite regulation at sites of inflammation, likely because of opposite regulation by the pro-inflammatory cytokines IL-1 and TNF- α , with up-regulation of 11 β -HSD1 and down-regulation of 11 β -HSD2 (reviewed in [12]), suggesting they modulate local glucocorticoid action during inflammation (Fig. 1a). 11 β -HSD1 is expressed in immune cells, including macrophages and lymphocytes. Its expression, by-and-large, is increased following immune cell activation. In contrast, 11 β -HSD2 is not normally expressed in immune cells, though it may become expressed in human macrophages and possibly other mononuclear cells in certain pathological situations [79], suggesting resistance to endogenous glucocorticoids under these circumstances.

Unsurprisingly, given the well-known effects of glucocorticoids in limiting acute inflammation, 11 β -HSD1-deficiency in mice increases the severity of acute inflammation. Inflammation is increased in an experimental model of arthritis, and more neutrophils and monocytes/macrophages are elicited in sterile peritonitis and pleurisy, consistent with a mechanism in which early induction of 11 β -HSD1 during inflammation limits the severity of the response. 11 β -HSD2-deficiency has no effect [80]. Similarly, following coronary artery ligation, more neutrophils and monocyte/macrophages are recruited in hearts of 11 β -HSD1-deficient mice [81]. This contrasts with the attenuated inflammation that occurs in adipose tissue of 11 β -HSD1-deficient mice during diet-induced obesity, with reduced macrophage and T cell infiltration of visceral adipose tissue [82].

Plausibly, an increased angiogenic response to hypoxia may be the common link in the beneficial effects of 11 β -HSD1 inhibition or deficiency in metabolic disease (reviewed in [12]). Angiogenesis *in vivo* and *in vitro* is increased with 11 β -HSD1-deficiency [83]. This results in better recovery of heart function following myocardial infarction in 11 β -HSD1-deficient mice, despite (or possibly because of) greater inflammation acutely following coronary artery ligation [81, 83]. A similar increase in angiogenesis likely underlies the reduced hypoxia and inflammation within adipose tissue of high fat-fed 11 β -HSD1-deficient mice [84]. Moreover, although it has not been tested in 11 β -HSD1-deficient mice, angiogenesis is implicated in the pathogenesis of rheumatoid arthritis [85].

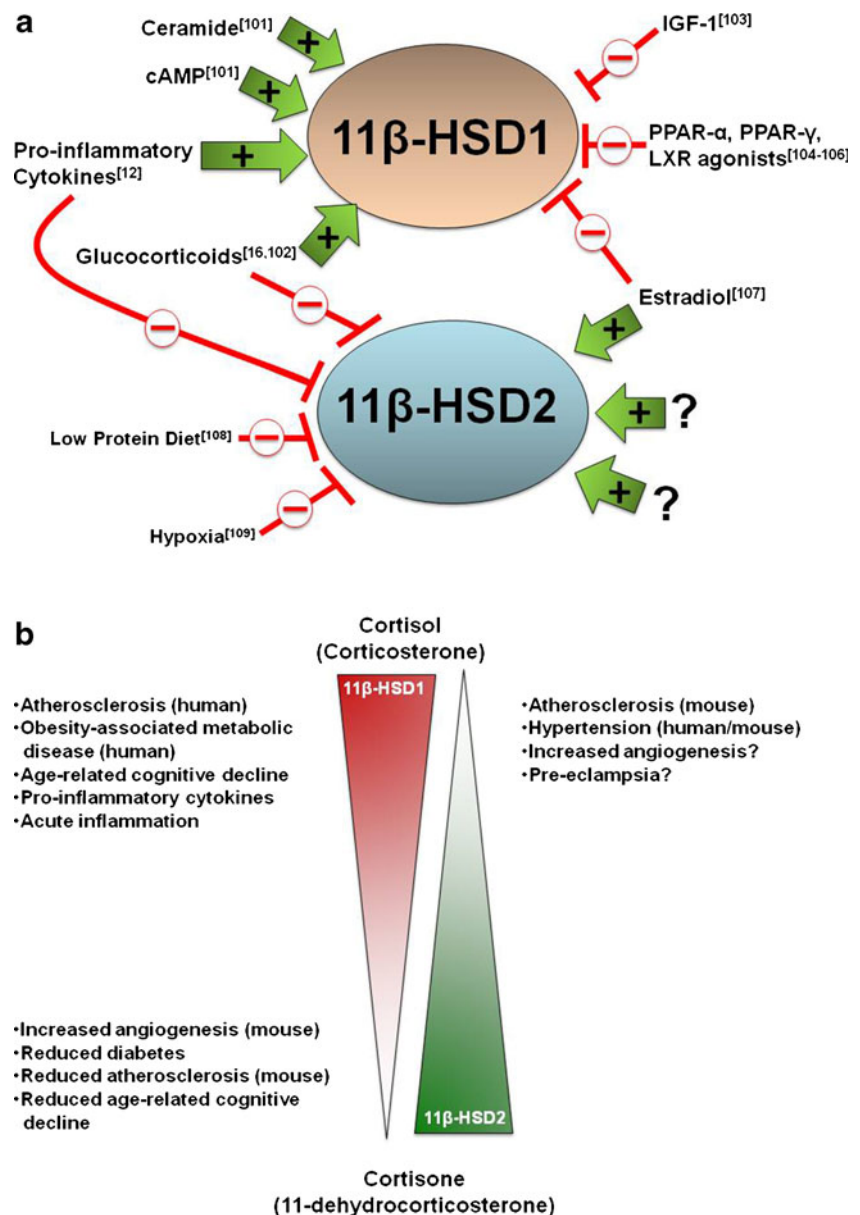
11 β -HSD2 may regulate angiogenesis in human endometrium, in the opposite manner. Higher endometrial 11 β -HSD2 expression is associated with heavy menstrual bleeding, plausibly due to reduced thrombospondin-1-mediated inhibition of angiogenesis as a result of greater cortisol inactivation [86]. Importantly, these 11 β -HSD actions are entirely consistent with the known actions of glucocorticoids, which limit acute inflammation whilst provoking adverse inflammatory cardiometabolic states. Whilst glucocorticoids promote adaptation, including tissue remodelling when homeostasis is perturbed, they are also strongly anti-angiogenic both *in vivo* and *in vitro* [83].

11 β -HSDs as a Therapeutic Target in Atherosclerosis

Levels of 11 β -HSD1 mRNA are increased in human atherosclerotic vessels compared either with nearby intact (atheroma-free) vasculature or with vessels from control patients without coronary artery disease [87, 88]. This may reflect a pro-inflammatory peri-vascular environment in disease rather than systemic inflammation; mRNA levels of both 11 β -HSD1 and CD68 (a macrophage marker) are increased in epicardial adipose tissue of patients with coronary artery disease compared with controls [87], consistent with inflammation within the peri-vascular adipose tissue associated with vascular inflammation. Pro-inflammatory cytokines increase 11 β -HSD1 expression (Fig. 1a) in human and murine vascular smooth muscle cells *in vitro* [89, 90], but acute systemic inflammation has little or no effect on vascular 11 β -HSD1 expression in mice [90]. This situation, with locally increased 11 β -HSD1, is similar to that associated with inflammation in adipose tissue of metabolic syndrome patients. It suggests that dysregulated vascular 11 β -HSD1, possibly initially induced to control local inflammation within the vasculature, might then drive local inflammation both within the vasculature and in the surrounding adipose tissue by restricting angiogenesis, thus promoting a hypoxic environment. This, of course, points to 11 β -HSD1 inhibition as an attractive target in atherosclerosis. Dysregulation of 11 β -HSD2 in human arterial disease has not been described (Fig. 1a), but the opposite regulation of 11 β -HSD2 by pro-inflammatory cytokines is predicted to decrease levels within endothelial cells, allowing cortisol activation of MR and its pro-inflammatory consequences, given a setting of high levels of systemic risk factors (see below).

The potential for 11 β -HSD1 inhibition as an effective pharmacotherapy for atherosclerosis was demonstrated by Hermanowski-Vosatka and colleagues from Merck [91]. Compound 544, a selective 11 β -HSD1 inhibitor, modestly reduced circulating cholesterol levels and markedly reduced intra-aortic cholesterol in atherosclerosis-prone *ApoE*^{-/-} mice fed a cholesterol-enriched 'western diet' [91]. More

Fig 1 Regulation of 11 β -hydroxysteroid dehydrogenase isozyme activity in health and disease. **(a)** The biochemical pathways that regulate 11 β -HSDs. A number of factors have been identified that selectively increase (green arrows) or decrease (red lines) 11 β -HSD isozyme expression [101–109]. Note: only some of the biochemical pathways that regulate 11 β -HSD expression are shown; factors that may affect 11 β -HSD activity (eg. glucose-6-phosphate availability, hexose-6-phosphate dehydrogenase activity [110] and insulin signaling) are not shown. Little is known about the pathways that regulate 11 β -HSD2 activity in the vasculature. **(b)** The relationship between 11 β -HSD isozyme activity and disease pathologies. High (top left) and low (bottom left) activity of 11 β -HSD1, and low activity of 11 β -HSD2 (top right) are all associated with disease pathologies



recently, this group has shown a similar reduction in intra-aortic cholesterol with a distinct inhibitor (Compound L-750), without effects on plasma lipids in *Apoe*^{-/-} mice [67•]. However, another study in triple knock-out mice (lacking the LDL receptor, apolipoprotein-b and leptin) with a different selective inhibitor (Compound 2922), reported no effect on atherosclerosis and only slightly reduced plasma LDL levels, despite improved glucose homeostasis [92]. A previous study in *Ldlr*^{-/-} mice with the non-selective inhibitor, carbenoxolone, only showed an effect on plasma lipids and atherosclerosis in severely obese mice (due to an additional mutation in the *Agouti* gene), though the drug treatment is likely to have made the mice hypertensive through inhibition of 11 β -HSD2 (blood pressure was not reported) [93]. More recently, we have shown that generating either homozygous or heterozygous *Hsd11b1* deletion and, thus,

11 β -HSD1-deficiency (avoiding possible off-target drug effects) attenuates atherosclerosis in *Apoe*^{-/-} mice without affecting plasma glucose or lipid levels. This suggests that atheroprotection in this background is not simply due to improvements in systemic risk factors, although it should be noted that the contribution of hemostatic factors has not been addressed. Reconstitution of lethally irradiated *Apoe*^{-/-} mice with bone marrow from *Hsd11b1*^{-/-} *Apoe*^{-/-} mice similarly reduced atherosclerosis compared to controls reconstituted with *Apoe*^{-/-} donor bone marrow, implicating 11 β -HSD1-deficiency in haematopoietic cells in the mechanism, and suggesting that any differences in plasma glucocorticoid turnover in 11 β -HSD1-deficient mice [74, 94] are unlikely to be critical. The converse situation occurs with 11 β -HSD2-deficiency, which accelerates atherosclerosis and worsens vascular inflammation in *Apoe*^{-/-} mice

independent of effects on blood pressure, even without the stimulus of western diet [13•]. Importantly, this suggests that it is intravascular glucocorticoid action that is the main culprit in 11 β -HSD2-deficient *Apoe*^{-/-} mice, rather than deficiency in the surrounding adipose tissue or circulating immune cells; 11 β -HSD2 is not normally expressed either in immune cells or in adipose tissue, though inflammation within peri-vascular adipose tissue could, of course, contribute to pathology once initiated. A summary of experimental studies describing the effects of 11 β -HSD inhibition or deficiency on atherosclerosis/vascular inflammation is shown in Table 1. Interestingly, neither 11 β -HSD1- nor 11 β -HSD2-deficiency affected neointimal proliferation following femoral artery wire injury in lean healthy mice, though it was reduced by 11 β -HSD1-deficiency in *Apoe*^{-/-} mice (*Hsd11b2*^{-/-} *Apoe*^{-/-} double knock-out mice were not tested) [95]. Thus, 11 β -HSD1-inhibition is only likely to be effective in reducing neointimal proliferation when concurrent with exaggerated systemic risk factors.

Mechanism of Action of 11 β -HSD Manipulation

The mouse studies suggest at most a modest contribution of systemic risk factors to the effects of 11 β -HSD deficiency or inhibition upon atherosclerosis, pointing instead to effects within both immune cells (11 β -HSD1) and the vasculature (11 β -HSD2). As stated above, immune cells are implicated as a target. Although macrophage density appears unaltered with 11 β -HSD1-deficiency, T cell infiltration is reduced [96•] and 11 β -HSD1 inhibition, either prophylactically or therapeutically in established atherosclerosis, reduces expression of pro-inflammatory and cell adhesion molecules in the vasculature of *Apoe*^{-/-} mice [70, 96•]. Interestingly, the microarray studies on vasculature also highlight suppression of mRNAs encoding coagulation factors by 11 β -HSD1, something that warrants further investigation. Experimental studies have implicated the coagulation system in the pathogenesis of atherosclerosis and atherothrombosis (reviewed in [97]) and megakaryocytes, the precursors to platelets, would be transferred in the bone

Table 1 Experimental studies describing the effects of 11 β -HSD inhibition or deficiency on vascular inflammation

| 11 β -HSD1 inhibition/deficiency | Species | Outcome | Ref |
|--|--|--|-------|
| 11 β -HSD1 inhibitor (Compound 544) | <i>Apoe</i> ^{-/-} mice | ↓ atherosclerosis ↓ circulating cholesterol ↓ circulating MCP-1 | [91] |
| 11 β -HSD1 inhibitor (Compound L-750) | <i>Apoe</i> ^{-/-} mice | ↓ atherosclerosis ≠ circulating lipids ↓ circulating MCP-1 and aortic MCP-1 mRNA expression ↓ expression of: inflammatory, adhesive and coagulation factors in the vasculature | [67•] |
| 11 β -HSD inhibitor (Compound 2922) | <i>Ldlr</i> ^{-/-} <i>Apob</i> ^{100/100} <i>Lep</i> ^{ob/ob} mice | ≠ atherosclerosis ↓ circulating LDL improved glucose homeostasis | [92] |
| 11 β -HSD inhibitor Carbenoxolone (inhibits both isozymes) | <i>Ldlr</i> ^{-/-} <i>Agouti</i> ^{-/-} mice | ↓ atherosclerosis in severely obese mice (additional <i>agouti</i> mutation) ↓ circulating lipids | [93] |
| 11 β -HSD1 inhibitor (Compound 544) | <i>Apoe</i> ^{-/-} mice | ↓ atherosclerosis ≠ fasting plasma cholesterol, triglycerides or NEFA ↑ plaque stability | [96•] |
| 11 β -HSD1 deficiency | <i>Hsd11b1</i> ^{-/-} <i>Apoe</i> ^{-/-} mice | ↓ atherosclerosis ≠ circulating lipids ↓ circulating MCP-1 ↓ circulating Ly6C ^{hi} monocytes ≠ macrophage density into lesions ↓ T cell infiltration into lesions ↓ aortic VCAM-1 mRNA expression ↓ atherosclerosis in irradiated <i>Apoe</i> ^{-/-} mice receiving bone marrow cells from <i>Hsd11b1</i> ^{-/-} <i>Apoe</i> ^{-/-} donor mice | [96•] |
| 11 β -HSD2 deficiency | <i>Hsd11b2</i> ^{-/-} <i>Apoe</i> ^{-/-} mice | ↑ atherosclerosis ≠ blood pressure | [13•] |

≠ no significant effect, ↓ reduced, ↑ increased, NEFA: non-esterified fatty acids

marrow reconstitution experiments that implicate immune cells [96•].

Western diet-induced monocytosis is attenuated with 11 β -HSD1-deficiency in *Apoe*^{-/-} mice, attributable to the pro-inflammatory Ly6C^{hi} monocyte subset. Instead, monocytes are retained in the bone marrow and spleen of *Hsd11b1*^{-/-}*Apoe*^{-/-} mice [96•]. Lower circulating levels of MCP-1, the main macrophage chemoattractant in atherosclerosis [98], in *Hsd11b1*^{-/-}*Apoe*^{-/-} mice are implicated in this difference [67•, 91, 96•], though whether the MCP-1 originates from the vasculature or adipose tissue is currently unclear [67•, 96•]. Either way, circulating MCP-1 is unlikely to be the sole or even the main target of 11 β -HSD1-deficiency/inhibition.

Plausibly, the opposite effects of deficiency in 11 β -HSD1 or 11 β -HSD2 activity upon atherosclerosis reflect different but complementary mechanisms. 11 β -HSD2 is not expressed in mouse immune cells, but it is expressed in vascular endothelial cells, where it restricts activation of MR by glucocorticoids. In mouse aortic endothelial cells in vitro, vascular cell adhesion molecule-1 was induced by corticosterone in an MR-dependent manner, but only following inhibition of 11 β -HSD2. In vivo, antagonism of MR with eplerenone, at doses which had no effect on blood pressure, attenuated lesion development and inflammation, whilst also increasing collagen and smooth muscle content, markers of plaque stability [13•]. Together, these data clearly suggest that preservation of vascular endothelial cell 11 β -HSD2 activity is important in controlling vascular injury and subsequent inflammation.

The target of 11 β -HSD1-generated ligand is less obvious. Although GR has long been known to shape macrophage phenotype, recent evidence has also shown a crucial role for MR in governing macrophage polarisation, with MR-deficient macrophages skewing towards a "pro-resolution" alternatively activated (or M2) phenotype [99]. In vivo, MR deficiency in macrophages alone is sufficient to protect against the vascular damage and cardiac hypertrophy and fibrosis induced by L-NAME and angiotensin II [99], consistent with pro-inflammatory MR activation by glucocorticoids (11 β -HSD2 is absent from macrophages). However, the high affinity MR is predicted to be activated even at basal plasma glucocorticoid levels, and these are normal in 11 β -HSD1-deficient mice [94]. 11 β -HSD1 may therefore amplify ligand availability to GR. But GR activation in macrophages would be expected to promote a pro-resolution phenotype. Exactly how intracellular glucocorticoid activation of MR versus GR is achieved in cells that express both without 11 β -HSD2 is currently unclear [99], but could conceivably involve GR:MR heterodimers [100] and might be critical in pro- and anti-inflammatory actions of endogenous glucocorticoids. An alternative target is GR in megakaryocytes, but whether 11 β -HSD1 is even expressed in these cells is unknown. Future dissection of the cellular and molecular targets will require selective receptor antagonism,

as well as tissue-specific disruption of the 11 β -HSD1 gene in mice, to elucidate specific roles in key processes during inflammation and angiogenesis.

Conclusions

There is clearly a counterbalance between the pro-atherogenic effects of 11 β -HSD1 activity and the atheroprotective effects of 11 β -HSD2 activity during vascular inflammation (Fig. 1b). Any therapy based on manipulation of glucocorticoid metabolism should inhibit 11 β -HSD1 activity whilst preserving 11 β -HSD2 activity. Future work should concentrate on elucidating whether the cellular and molecular targets are indeed complementary or may be overlapping. New drug delivery methods [41], targeting macrophages or indeed other cell types, open up exciting new therapeutic possibilities in vascular inflammation and atherosclerosis.

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Conflicts of Interest Patrick WF Hadoke declares no conflicts of interest.

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Jonathan R. Seckl has been a consultant for several commercial drug development programmes for 11 β -HSD1 inhibitors.

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